BHJ 278/78 *Br Heart J* 1981; **45**: 649–55

Prinzmetal's angina with documented coronary artery spasm
*Treatment and follow-up**

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SUMMARY Eighteen patients with Prinzmetal's angina were studied angiographically and 17 were followed for an average of 27 months. There were 12 men and six women, with a mean age of 46·3 years. The mean duration of symptoms before clinical diagnosis was 4·1 weeks. Four had had a previous myocardial infarction. Six patients had spontaneous cardiac arrests within 48 hours of diagnosis and hospital admission. At coronary arteriography, 10 patients had significant coronary artery disease; two of these had coronary artery spasm. The remaining eight patients had normal coronary arteries with significant coronary artery spasm at arteriography. Angiographic mitral valve prolapse was found in eight patients; seven of these had inferior ST segment elevation with pain. Six of the 10 patients with significant coronary artery disease had aortocoronary bypasses performed with good results. Ten of the remaining 11 patients who were treated medically had their symptoms controlled with oral isosorbide dinitrate alone or in combination with propranolol, nifedipine or perhexiline but propranolol may have an adverse effect. Though the initial clinical course in untreated patients was unfavourable, progress after starting treatment was good, with no further cardiac arrests, myocardial infarctions, or deaths.

Prinzmetal[1] described a variant form of angina characterised by cyclical rest pain, often severe, prolonged, and nocturnal in character with transient ST segment elevation. This variant form of angina was sometimes associated with ventricular arrhythmias.[2] We review the presentation, investigation, and clinical course of 18 consecutive patients with this diagnosis to determine their clinical outcome and result of treatment.

Patients and methods

Over a four-year period, 18 patients fulfilling Prinzmetal's original criteria[2] were diagnosed as having variant angina. Each had one or more episodes of chest pain with documented electrocardiographic ST segment elevation (Fig. 1) while in hospital. All had left ventricular angiography and coronary arteriography by the Judkins technique. Selective coronary arteriograms were performed in multiple projections, including cranial and caudal angulations,[3 4] and the left ventricular angiogram was performed in a 30° right anterior oblique view. No glyceryl trinitrate was administered before cardiac catheterisation. After coronary arteriography, with or without prior ergonovine maleate provocation, sublingual glyceryl trinitrate (0·6 mg) was administered to all patients to determine whether lesions were fixed or resulted from spasm. The left ventricular angiogram and selective coronary arteriograms were recorded on 35 mm cineangiographic film at 30 frames per second; they were interpreted independently by three observers unaware of the patient's clinical diagnosis. Seventeen of the 18 patients were followed up. The clinical status of each patient was assessed and a record made of the drug treatment. The patients' reports of symptoms and treatment were all verified with their primary physicians.

Results

CLINICAL DATA (Table 1)

There were 12 men and six women. The mean age of the 18 patients was 46·3 years. Four patients had

*Supported in part by the Canadian and Ontario Heart Foundations.

Received for publication 22 July 1980

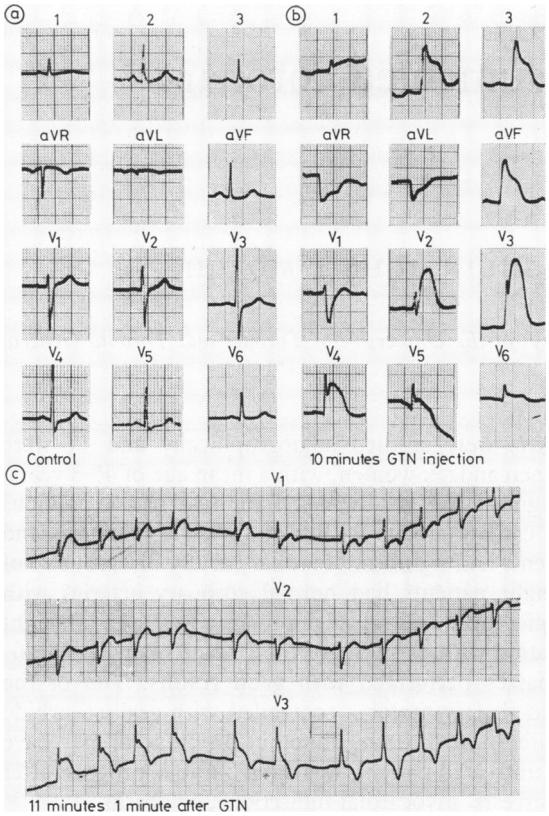

Fig. 1 *12 lead electrocardiograms of case 14 at rest: control (1a) and after ergonovine administration (1b) in doses of 0·05, 0·10, and 0·25 mg at two minute intervals. Electrocardiographic changes occurred only after the third dose of ergonovine. The rhythm strip (1c) was recorded after glyceryl trinitrate. There is significant ST segment elevation in both the inferior and anterior leads. This patient had focal right and diffuse left coronary artery spasm shown at arteriography both spontaneously and after ergonovine administration.*

had a myocardial infarction (three anterior and one inferior) before the onset of Prinzmetal's angina. There was no correlation between the site of this myocardial infarction and the subsequent ST segment elevation.

Symptoms were present from one to eight weeks (average 4·1 weeks) before the patients were clinically diagnosed as having variant angina. The patients were classified on the basis of the site of ST segment elevation. This elevation was considered "inferior" when it occurred in leads II, III, and aVF, and "anterior" when it occurred in the praecordial leads. Thirteen patients had inferior, four anterior, and one both inferior and anterior ST segment elevation during episodes of chest pain. After the clinical diagnosis of variant angina, six patients, all not receiving antiarrhythmic treatment, had spontaneous ventricular arrhythmias requiring resuscitation within 48 hours of admission to hospital. These ventricular arrhythmias occurred during spontaneous pain while the patients were awaiting cardiac catheterisation. Four of these patients had inferior and two anterior ST segment elevation (Table 1). In no patient was a subsequent myocardial infarction detected by serum enzyme rises or permanent electrocardiographic changes. This held true regardless of whether or not the patient had experienced a cardiac arrest.

ANGIOGRAPHIC DATA (Table 2)

Ten of the 18 patients had significant (>70%) narrowing of one or more coronary arteries, two had 50 per cent obstruction of the left anterior descending coronary artery, and six had normal coronary arteries. Coronary artery spasm was shown in 10 patients during coronary arteriography, and two of them had significant coronary artery disease. In all 10 patients the spasm was relieved by sublingual glyceryl trinitrate. Two patients had mild to moder-

Table 1 *Clinical information*

Case no.	*Age (y)*	*Sex*	*Duration of symptoms (wk)*	*Site of ST elevation*	*Cardiac arrest*
1	39	M	8	Inferior	−
2	41	M	4	Inferior	+
3	38	M	4	Inferior	+
4	44	M	4	Inferior	−
5	48	M	3	Inferior	−
6	36	F	8	Anterior	−
7	55	M	2	Inferior	−
8	64	F	2	Anterior	−
9	35	M	8	Inferior	−
10	40	F	8	Inferior	−
11	45	F	4	Inferior	−
12	41	F	3	Inferior	+
13	60	M	1	Inferior	−
14	52	M	3	Anterior and inferior	−
15	44	M	1	Anterior	+
16	53	F	4	Inferior	+
17	51	M	3	Inferior	−
18	48	M	4	Anterior	+

Table 2 *Angiographic findings*

Case No.	*Mitral prolapse*	*Coronary artery (% stenosis)*	*Coronary artery spasm*	*Cause of spasm†*
1	+	90% right coronary	—	—
2	−	95% right coronary	—	—
3	+	95% right coronary, 75% left anterior descending	—	—
4	−	90% right coronary, 90% left anterior descending, 100% circumflex	—	—
5	−	100% right coronary, 75% left anterior descending	—	—
6	+	75% left anterior descending	100% left anterior descending	Spontaneous
7	+	50% left anterior descending	90% left anterior descending, 90% circumflex	Pacing
8	−	90% left anterior descending	—	—
9	+	—	70% right coronary	Spontaneous
10	+	—	90% right coronary	Spontaneous
11	−	75% right coronary	—	—
12	−	90% left anterior descending, 75% circumflex	100% right coronary	Spontaneous
13	−	90% left anterior descending	—	—
14	−	50% left anterior descending	100% right coronary, 90% left anterior descending	Spontaneous + ergonovine* (0·05, 0·10, 0·25 mg)
15	−	—	75% left anterior descending	Spontaneous
16	+	—	100% right coronary, 75% left anterior descending	Spontaneous + ergonovine (0·05 mg)
17	+	—	90% right coronary	Ergonovine (0·05, 0·10 mg)
18	−	—	75% left anterior descending, 75% circumflex	Spontaneous + ergonovine (0·10, 0·20, 0·40 mg)

*Ergonovine maleate. + = mitral valve prolapse present.
†Figures represent dose of ergonovine maleate administered parenterally during cardiac catheterisation with two minutes between doses.

ate coronary artery disease (50% narrowing of the left anterior descending coronary artery) while the remaining six had normal coronary arteries. In eight patients the spasm occurred spontaneously, while in one it only occurred after provocation with ergonovine maleate. In the 10th patient (case 7) coronary artery spasm was provoked by right atrial pacing.[5] Fig. 1 shows distinct ST segment elevation in both the inferior and anterior leads of case 14 who had ergonovine maleate-provoked spasm of both coronary arteries. Fig. 2 and 3 are examples of focal spasm of the right coronary artery and diffuse spasm of the left coronary artery in this patient. Fig. 4 and 5 are examples of ergonovine-induced focal and diffuse spasm of the proximal and mid right coronary artery. The ergonovine maleate was administered in incremental doses from 0·05 to 0·40 mg. Increasing doses of ergonovine produced increasing

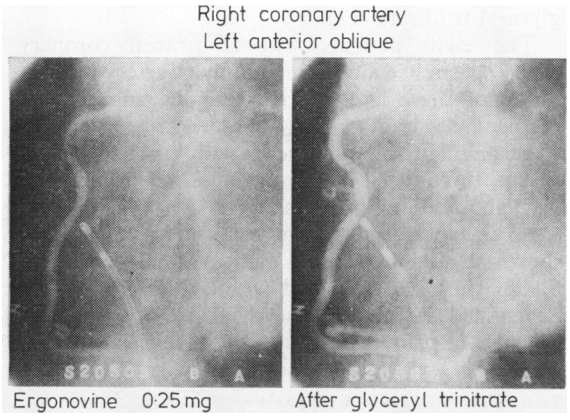

Fig. 2 *Right coronary arteriogram of case 14 in the right anterior oblique view after ergonovine and glyceryl trinitrate administration. There is severe focal proximal spasm of the right coronary artery.*

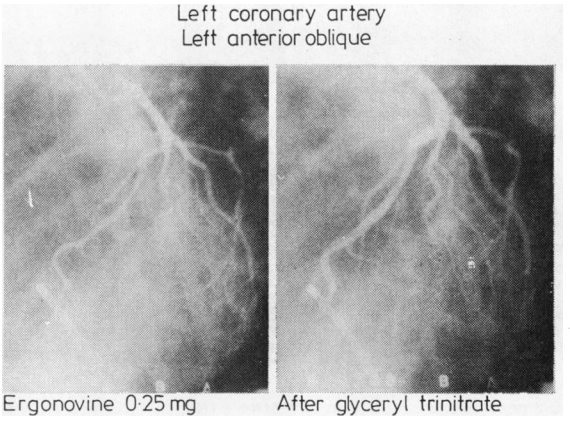

Fig. 3 *Left coronary arteriogram of case 14 in the left anterior oblique view after ergonovine and glyceryl trinitrate administration. With ergonovine there is severe diffuse spasm of the left coronary artery.*

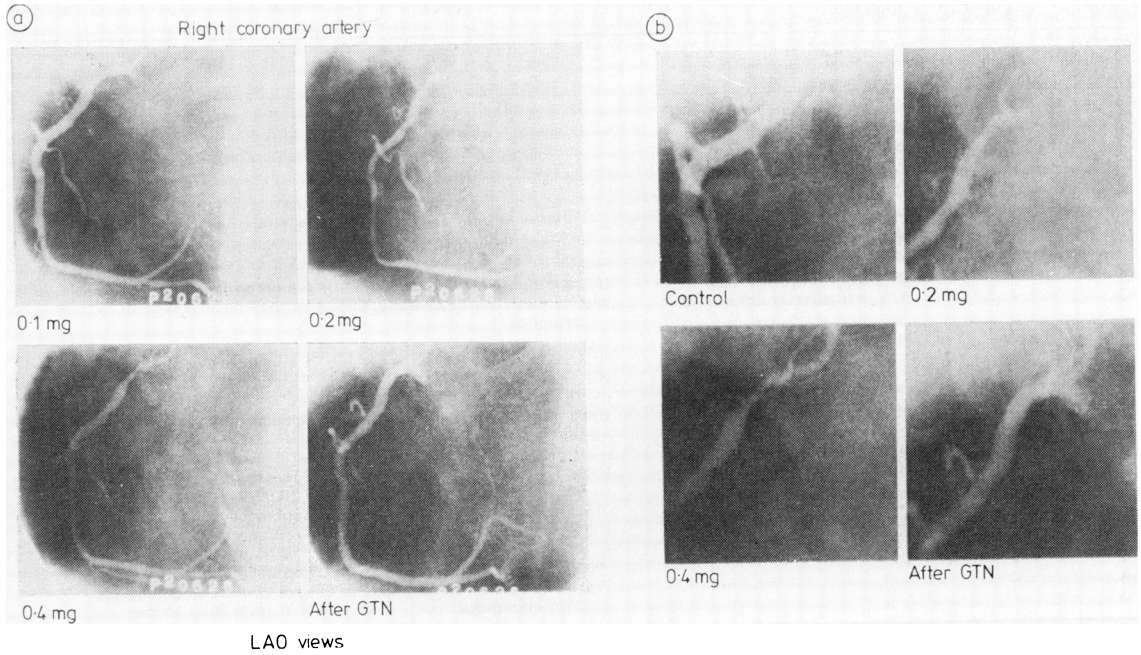

Fig. 4 *Complete right coronary arteriograms (4a) and proximal right coronary artery (4b) of case 16 showing progressively increasing spasm of the proximal right coronary artery with increasing doses of ergonovine.*

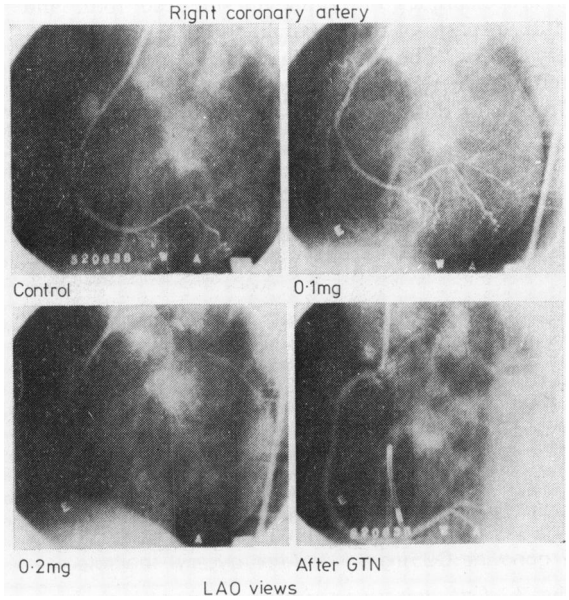

Fig. 5 *Right coronary arteriogram of case 17 showing complete occlusion of the vessel with ergonovine administration.*

degrees of spasm of the proximal right coronary artery in the patient shown in Fig. 4. Two patients who had spontaneous pain also had spasm provoked by parenteral ergonovine maleate. It was possible to relieve both spontaneous and pharmacologically-provoked coronary artery spasm with sublingual glyceryl trinitrate (Fig. 1).

The eight patients without proven coronary artery spasm had significant coronary artery disease. Seven of these had inferior and one anterior ST segment elevation during spontaneous episodes of chest pain. In the 10 patients with coronary artery spasm, three had ST elevation anteriorly, six inferiorly, and one in both sites.

An unexpected finding was mitral valve prolapse shown angiographically in eight patients (Table 2). Six of these patients had coronary artery spasm. Seven had inferior ST segment elevation during episodes of pain.

TREATMENT AND FOLLOW-UP (Table 3)

Of the 10 patients with coronary artery disease (fixed narrowing $>70\%$), six had aortocoronary bypass surgery. Four had single and two had double aortocoronary bypass grafts. All six patients

Table 3 *Treatment and follow-up*

Case No.	*Duration of follow-up (mth)*	*Frequency of pain*	*Drugs* (oral)*	*Comments*
1	42	None	None	Right coronary artery to aortocoronary bypass, adventitia stripped
2	43	None	None	Right coronary artery to aortocoronary bypass, prior inferior myocardial infarction
3	59	None	None	Right coronary artery to aortocoronary bypass, left anterior descending coronary artery to aortocoronary bypass
4	46	None	Iso 40	Right coronary artery to aortocoronary bypass, prior anterior myocardial infarction, aneurysmectomy
5	36	None	Iso 80, Pro 80	Right coronary artery to aortocoronary bypass, left anterior descending coronary artery to aortocoronary bypass
6	11	None	None	Left anterior descending coronary artery to aortocoronary bypass
7	21	None	Iso 300	—
8	22	None	Iso 160	Prior anterior myocardial infarction
9	20	None	None	—
10	57	Occasional	Iso 40	—
11	LTF	LTF	LTF	—
12	19	Occasional	Iso 30	Prior anterior myocardial infarction
13	32	None	Iso 40	—
14	15	Frequent	Iso 160, Pro 240	Controlled on nifedipine 100 mg t.i.d.
15	18	None	Iso 60	—
16	7	Frequent	Iso 240, Pro 240	Controlled on perhexiline maleate 200 mg b.i.d.
17	7	None	Iso 240	—
18	8	None	Iso 120, Pro 40	—

Abbreviations: Pro, propranolol; LTF, lost to follow-up; Iso, isosorbide dinitrate.
*Figures represent total daily dose of each drug which was given in divided doses q.i.d.

remained free of pain during the follow-up period. Four of them are on no drugs, but one is having oral isosorbide dinitrate, and another a combination of oral isosorbide dinitrate and propranolol because of persistent pain after operation. Of the 11 remaining patients available for follow-up, 10 were on medical treatment (Table 3)—oral isosorbide dinitrate alone or in combination with propranolol. The doses in Table 3 are daily totals actually administered in divided doses four times a day. Seven of the 11 medically treated patients were asymptomatic, two had occasional (weekly or less), and two multiple daily attacks of severe angina.

The two severely symptomatic patients, who were followed beyond the completion of this study, were receiving 240 mg propranolol daily in divided doses. In both cases, when the propranolol was discontinued, there was a dramatic *decrease* in frequency and severity of symptoms (*vide infra*). Neither patient became pain free on oral isosorbide dinitrate alone and each required additional drugs (nifedipine 100 mg t.i.d. or perhexiline 200 mg b.i.d.) to become pain free.

Discussion

Attacks of Prinzmetal's angina have been reported to be provoked by a variety of physiological and pharmacological stimuli including the cold pressor test,[6] drinking ice water,[7] alcohol,[8] REM sleep,[9] atrial pacing,[5 10] and exercise stress testing.[11–13] Our patients were studied before ergonovine maleate was in general use. In four patients, however, spasm was pharmacologically induced with parenteral ergonovine maleate in doses ranging from 0·05 to 0·40 mg. In each of these it was possible to reverse the spasm by the use of sublingual glyceryl trinitrate, as reported in other studies.[14–16]

In eight of the 18 patients a diagnosis of mitral valve prolapse was made angiographically by three independent observers who were unaware of the patient's clinical diagnosis. The presence of mitral valve prolapse may represent unusual patient selection or patterns of referral. It may also be possible that the prolapse is secondary to papillary muscle dysfunction because seven of the eight cases occurred in patients with inferior ST segment elevation on a surface electrocardiogram.[17] Four of these seven cases had documented right coronary artery spasm. Further investigation is necessary to determine whether this finding is causative or merely coincidental or indeed whether on the contrary patients with prolapse have a predisposition to coronary artery spasm. An increased incidence of mitral valve prolapse in the presence of acute myocardial infarction with normal coronary arteries and coronary artery spasm has been reported.[17–19]

The use of oral isosorbide dinitrate was effective in 10 of the 12 patients (including two of the surgically treated group) who continued to have attacks of Prinzmetal's angina. Four of the six surgically treated patients were pain free without

drugs. The two patients whose symptoms were not controlled by oral isosorbide dinitrate alone required nifedipine or perhexiline to do so. Both were also receiving propranolol, as were two others without pain. This drug has been considered capable of inducing coronary artery spasm.[20] Yasue *et al.*[21] described four patients in whom Prinzmetal's angina increased after the administration of propranolol. In two of our patients Prinzmetal's angina decreased after stopping propranolol. Yasue *et al.*[22] considered coronary artery spasm in their patients to be mediated by unopposed alpha-adrenergic receptors The coronary vessels are richly innervated and coronary artery spasm can be induced by adrenergic nerve stimulation in the normal coronary artery bed of the dog.[23] Neurogenic vasoconstrictor impulses to the coronary vessels are transmitted through sympathetic nerves acting upon alpha-adrenergic receptors in the coronary vascular bed, suggesting a possible role for alpha-adrenergic receptor blocking agents in Prinzmetal's angina.[5 23]

It is important not to block vasodilator influences acting on the coronary vascular bed Stimulation of beta-2 receptors, which induces vasodilatation in coronary vessels, can be blocked by propranolol. Blockade with nonselective beta-blockers may actually be detrimental in patients in whom ischaemia is caused by decreased oxygen delivery secondary to coronary artery spasm rather than to augmented myocardial oxygen needs, since such blockade may allow the unopposed influence of coronary vasoconstrictor impulses to prevail.[23 24]

There are several reports reviewing the role of surgical treatment in patients with Prinzmetal's angina.[20 25–28] The majority of these recommend it only for patients with significant proximal coronary artery obstruction in addition to coronary artery spasm. In general, results of surgery have been less favourable in patients with Prinzmetal's angina than in patients with classical angina. Several of these papers described patients who died postoperatively and, at necropsy, were found to have patent vein grafts to the "spastic" vessel. As in other studies, our patients who benefited from surgical treatment had severe "fixed" proximal disease, and we would not, therefore, recommend surgery for spasm unless this is present.

The clinical course of these patients was poor without treatment. Six of the 18 patients had a cardiac arrest within five weeks of the onset of symptoms. Only two of these had mitral valve prolapse. The prognosis, however, was good once treatment was started and no further cardiac arrests, myocardial infarctions, or deaths occurred in 17 medically and surgically treated patients who have been followed for up to five years. Other follow-up studies have also suggested a good prognosis.[10 28–31]

In the majority of patients oral isosorbide dinitrate alone was effective in completely relieving symptoms. If oral isosorbide dinitrate is not effective in controlling symptoms then calcium antagonists, such as verapamil or nifedipine, may help. If stopping treatment with propranolol produces relief of rest angina associated with ST segment elevation, the diagnosis of coronary artery spasm must be considered. A corollary is that beta-blockade may be the reason why treatment is ineffective in some patients.

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